UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,974	06/20/2001	Mark Laurence Brader	X-11869	9992

7590 02/12/2004

Mark J Stewart
Eli Lilly and Company
Lilly Corporation Center/DC 1104
Indianapolis, IN 46285

EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,974	BRADER ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *37-39 and 44-46* is/are allowed.

6)☐ Claim(s) *27-36,40-43 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Finality of the Office Action mailed November 19, 2003 has been withdrawn.

2. Applicant's response to the Office Action mailed November 19, 2003 on January 20, 2004 is acknowledged.

Claim Disposition

3. Claims 27, 30, 32, 37, 39, 44 and 46 have been amended. Claims 27-47 are pending and are under examination.

4. The following grounds of rejection are or remain applicable:

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 27-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a shelf stable solution formulation comprising SEQ ID NO: 2 and GLP-1 analogs: 7-34; 7-35; 7-36; 7-37, does not reasonably provide enablement for " any one additional amino acid substitution at any position in the claimed sequence". Pages 9-10 of the instant specification describes specific residues that can be substituted at specific positions in the claimed sequence, however, claim 27 reads on any of the 20 amino acids at any position in the claimed sequence which could result in an unstable formulation and the specification does not describe or provide support for the breath of the claims. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to:

I. Quantity of Experimentation Necessary:

The claimed invention is directed to "a shelf stable solution formulation comprising GLP-1 contained in SEQ ID NO:2". The sequence can have specific substitutions at a R1, X, Y, Z or R2 position. However, the claim also recites that one additional amino acid substitution can occur in the sequence, however, neither the specification nor the claims provide any detail as to whether the substitution will again occur at the above variable positions or any where in the molecule. In addition, there is no indicia as to what residue substitution can be tolerated to retain stability and if the position of the residue will affect the formulation adversely. The specification provides on page 9-10 a discussion of GLP-1 analogs and derivatives, however, the substitutions contemplated is limited to specific residues at specific positions in the sequence. Therefore, a skilled artisan would have to engage in undue experimentation to be able to determine if all possible substitutions results in a shelf stable formulation and if there are positions within the molecule that cannot tolerate the modification contemplated, to practice the claimed invention commensurate in scope with the claims.

II. Amount of direction or guidance presented:

The specification does not disclose whether or not for example, a substitution of an alanine at position 3 would be detrimental to the formulation, thus the specification lacks adequate guidance/direction to be enabling.

III. Presence or absence of working examples:

The working examples provided do not demonstrate or describe the claimed invention to enable the scope of the claims.

IV. Nature of the Invention/ State of the prior art and Relative skill of those in the art/ Predictability or unpredictability of the art:

The nature of the invention relates to a stable formulation in solution comprising GLP-1 with substitutions of specific residues at a specified position. The claimed product can also have a substitution of one additional amino acid anywhere in the protein. The prior art teaches GLP-1 analogs, with substitutions that retain stability, however, no support was found for a substitution throughout the protein and having no adverse effect on the formulation. For example GLP-1 analogs (a molecule having one or more amino acid substitutions) are disclosed in WO 91/11457 and they include modification such as a substitution of glycine at position 26 or 34, and lists a number of substitutions that can also occur at positions 36, 31, 21, 22, 15, etc. Specific positions having specific residue substitutions are provided.

The prior art generally acknowledges that a structural change in a protein's sequence can affect the function of the protein. Tuddenham et al. (Nucleic Acids Research, vol. 22, no. 17, pages 3511-3533, 1994) teach that substitution of an amino acid such as alanine, as a result of the changes to the nucleotide sequence, have a significant functional impact on the polypeptide.

Therefore, the substitution of any amino acid at any position within SEQ ID NO:2 encompassed in claim 27, can result in an unstable product, rendering the invention as unpredictable. Since very little is known in the prior art about the nature of the invention renders the art unpredictable with respect to the substitution contemplated. The specification should then give more details as to how to make and use the invention in order to be enabling.

VII. Breadth of the claims:

The breadth of the claims are very broad and encompass any amino acid at any position and there is no guidance in the specification as to what residue and at what position would produce a formulation that is unstable or a demonstration that all residues at any position in the claimed sequence produces a stable formulation. Thus, for all these reasons the specification is not considered to be enabling and at the time of filing would not have taught one skilled in the art how to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 27-33 are rejected under 35 U.S.C. 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 and the dependent claims hereto remain indefinite because the claim recites "and further comprises one additional amino acid substitution" because it is unclear whether the variable X, Y, Z, R1 or R2 contains this additional substitution or if the substitution is a position separate from the listed variables. The claim language can also be interpreted as, having one additional substitution at any position in the sequence, it is unclear what residues will be substituted at what positions; and if all possible residues will result in a stable formulation. In addition, the structure of the protein is undefined/unknown as there is no indicia where the substitution and what residue is coming into SEQ ID NO:2.

Claim 28 is indefinite as the claim recites "about 8.2 to about 8.5" with regard to the pH range and the independent claim recites a pH range of "about 8.2 to about 8.8", note that claim 28 does not further limit claim 27 as the about language recited could result in the same pH range in both claims. Note also that the specification does not provide a definition for "about" thus, about could mean plus or minus three points from the given range. It is suggested that the word "about" be deleted in both claims or claim 28 is canceled.

Claim Rejections - 35 USC § 102/§ 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)). 7.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

8. Claims 27-29, 33-36, 40-43 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Hoffmann (U.S. Patent No. 6,358,924, March 2002).

Hoffmann teaches a stable solution formulation comprising GLP-1 peptides and GLP-1 analogs that are identical to the instant SEQ ID NO:2 and the formulation in the instant claims 27 and 41. The formulation taught by Hoffmann contains a pharmaceutically acceptable preservative (m-cresol) and a tonicity modifying agent (glycerin). The formulation by Hofmann contains GLP-1 analogs with the variables set forth in the instant claims 29 and 43. GLP-1 analogs are said to have one or more amino acid substitutions and Hoffmann teaches the substitutions in claim 34. Hoffmann discloses a formulation that has a pH range of 6.5 to 9.0,

more preferably 7 to 8 which falls within the recited range of about 8.2 to about 8.8 and about 8.2 to about 8.5 (claims 28, 35 and 42), see columns 1-5.

Hoffmann teaches the GLP-1 analogs (7-34, 7-35, 7-36, and 7-37), see instant claim 36 and columns 3-5 of the patent. Thus, the claimed invention is anticipated. In-so-far-as Hoffmann does not explicitly teach a method to treat diabetes by administering the formulation as set forth in claims 33 and 40, Hoffmann states that the patented formulation provides much greater convenience and compliance for diabetic patients and persons having other conditions in which treatment with a GLP-1-like molecule is indicated. It is further stated that the characteristics of the formulation (solution formulation stored for long periods of time) will make GLP-1 treatment more useful and widely available and Hoffmann teaches a method of treating conditions for which administering of GLP-1 is indicated. Therefore, it would have been obvious from the teaching of Hoffmann to develop a method to treat diabetes with the formulation. Thus, the claimed method is within the skill of the art and *prima facie* obvious.

9. Applicant's arguments filed January 20, 2004 have been considered. The rejection under 35 U.S.C. 112, second paragraph remains. Applicant states that the claim 27 has been amended to obviate this ground of rejection, however, the amendments did not address the issue raised that the claim encompasses an additional substitution and it is unclear what residues will occupy what positions and if the formulation will remain stable. Note that new grounds of rejections have been instituted under 35 U.S.C. 102 and 112, first and second paragraphs for the reasons stated above.

Conclusion

10. Claims 37-39 and 44-46 are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope Robinson whose telephone number is (703) 308-6231. The examiner can normally be reached on Monday and Wednesday-Friday from 9:00 am to 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low, can be reached at (703) 308-2923.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. The official fax phone number for Technology Center 1600 is (703) 308-4242. Please affix the examiner's name on a cover sheet attached to your communication should you choose to fax your response. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

Hope Robinson, MS

Patent Examiner

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER